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Deep Arterial Injury During Experimental Angioplasty: Relation to a Positive Indium-111–Labeled Platelet Scintigram, Quantitative Platelet Deposition and Mural Thrombosis

JULES Y. T. LAM, MD, FACC,* JAMES H. CHESEBRO, MD, FACC,*
PETER M. STEELE, MB, BS (HONS), FRACP,* MRINAL K. DEWANJEE, PHD,*
LINA BADIMON, PHD,† VALENTIN FUSTER, MD, FACC,† with the technical assistance of
JAMES M. BYRNE, HOLLY B. LAMB and BRENDA I. WENDLAND

Rochester, Minnesota and New York, New York

Although it is not clear why coronary occlusion and restenosis occur after successful coronary angioplasty, factors related to the procedure may influence early and late results. The possible adverse effects of a medial tear documented histologically and produced during balloon angioplasty of the common carotid arteries were studied in 30 fully heparinized (100 U/kg body weight) normal pigs. Scanning electron microscopy showed endothelial denudation and extensive platelet deposition in all dilated arterial segments. Visible macroscopic mural thrombus was present within an hour of the procedure in 29 (91%) of the 32 arteries that had a medial tear documented by histologic study; the tear produced an indium-111–labeled platelet deposition of 116.4 ± 26.5 × 10^6/cm^2 (mean ± SE) and total thrombotic occlusion in 2 arteries (4%). None of the 24 arteries without a medial tear had a thrombus, and the mean platelet deposition in that group was 7.0 ± 0.5 × 10^6/cm^2 ($p < 0.0008$). In 12 pigs scanned with a gamma camera, visible thrombus was associated with platelet deposition in excess of 20 × 10^6/cm^2 in 12 arteries, 9 of which had a positive indium-111–labeled platelet scintigram.

Thus, arterial angioplasty causes deep arterial injury, which appears to be a major cause of mural thrombosis, heavy platelet deposition, a positive indium-111–labeled platelet scintigram and acute arterial occlusion. A positive indium-111–labeled platelet scintigram was always associated with macroscopic thrombus of at least 20 × 10^6 platelets/cm^2 and underlying deep arterial injury.

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Percutaneous transluminal coronary angioplasty has proved to be a valuable and effective means of revascularizing the ischemic myocardium and may be the procedure of choice in some patients with coronary artery disease. Despite this advancement, however, the mechanism of pathophysiologic events after balloon angioplasty is incompletely understood, especially acute occlusion and early restenosis. Our preliminary observations (1) suggested that platelet-thrombus formation may contribute importantly to the pathogenesis of these dreaded sequelae, and we thought that the severity of arterial wall injury might have an important role.

Acute coronary occlusion is a major setback after coronary angioplasty. Of 3,079 patients from the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry, 151 had coronary occlusion and 122 (81%) of them had major complications described as myocardial infarction, emergency surgery or death (2); coronary artery dissection was detected angiographically in 67 of the 151 patients. Conversely, 30% of patients with angiographic coronary artery dissection had these major complications (2).

A tear into or splitting of the plaque is probably associated with every successful angioplasty (3,4). The depth and surface area of the tear and local shear forces are probably major factors in thrombus formation. A medial tear (through the internal elastic lamina) and mural thrombosis appear to be frequently associated (1) and may lead to acute occlusion, but are difficult to detect. Thus, we addressed this relation

From the *Division of Cardiovascular Disease and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota and the †Division of Cardiology, Mount Sinai Medical Center, New York, New York.
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Address for reprints: James H. Chesebro, MD, Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55905.

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between a medial tear and acute platelet-thrombus deposition in a larger number of pigs and the ability to detect this mural thrombus formation with indium-111–labeled platelet scintigraphy. Although indium-111–labeled platelet scintigraphy can identify platelet thrombi formed after angioplasty in peripheral arteries in human patients (5), the extent of platelet deposition and mural thrombosis required to produce a positive in vivo indium-111–labeled platelet scintigram and the relation of platelet deposition and thrombosis to an intimal tear extending into the media after arterial angioplasty are unknown and are thus assessed in this study.

Methods

The study involved 30 normal 4 month old pigs of average weight (35 kg). The pigs were a mixture of Landrace, Yorkshire, Hampshire and Duroc breeds. They were housed at the Mayo Institute Hills Farm and were fed a normal chow diet. In all pigs, autologous platelets were labeled with 300 to 400 μCi of indium-111 tropolone (6) 18 to 24 hours before angioplasty.

Experimental protocol. The pigs were sedated with 300 mg of ketamine (Ketaset, Bristol) given intramuscularly. After inhalation of ether (ether USP, J. T. Baker), the pigs were intubated, mechanically ventilated with room air by a Harvard respirator and maintained anesthetized with 0.5% halothane (Fluothane, Ayerst Laboratories). The electrocardiogram and intraarterial pressure were continuously monitored throughout the procedure. Immediately after catheter insertion, a bolus of heparin (100 USP units/kg) was administered intravenously. Partial thromboplastin time was determined before heparin administration and again immediately before the animal was sacrificed.

An 8F balloon dilation catheter (Meditech polyethylene balloon, size 8 mm × 3 cm) was advanced under fluoroscopic control through a right femoral cutdown into the common carotid artery segment between the fifth and the fourth vertebrae (5 to 6 mm diameter). Five inflations were performed, 30 seconds each at 6 atm (Meditech pressure manometer), with 60 seconds between inflations.

Scintigraphic imaging. After dilation of both common carotid arteries in 12 pigs, anesthesia was maintained during imaging directly over the neck of the pig with a gamma camera (Pho-gamma V, Searle Laboratories) fitted with a medium energy, parallel hole collimator interfaced to a digital computer. Care was taken not to move the animal during the imaging procedure to allow direct subtraction of the blood pool scintigram (technetium-99m–labeled red blood cells) from the platelet-thrombus scintigram (indium-111–labeled platelets). The dilated arterial segment occupied less than 25% of the imaged region. Counts were accumulated for 20 minutes for the 247 keV photopeak of indium-111 radionuclide. The contribution of scattered indium-111 photons to the subsequent technetium-99m image was corrected for by a 5 minute image acquisition at the 140 keV setting. Two millicuries of technetium-99m–labeled red blood cells (7) were then injected intravenously, and after 3 to 5 minutes, the technetium-99m image was acquired for 5 minutes at the 140 keV photopeak.

The digitized indium, technetium and indium minus technetium images were interpreted as positive or negative by the consensus of three observers who were unaware of the other test results. Images were defined as positive for thrombus when there was a clearly abnormal localized indium excess in the blood pool substracted image.

Histopathologic and ultrastructural study. Next, the pigs were given an overdose of pentobarbital and an anterograde perfusion of 2% glutaraldehyde and 1% paraformaldehyde in 0.1 *M* cacodylate (pH 7.25) at a controlled pressure of 100 mm Hg for 15 minutes to fix the arteries in situ. The carotid arteries were then removed, cleaned and prepared for analysis. The location of the dilated portion of the fixed artery was easily identified after the in situ tissue fixation, which showed regions of vasoconstriction proximal and distal to the dilated area, and from spot films taken during and after angioplasty. The dilated portion of the fixed carotid artery was divided into two equal segments, and a similar-sized segment was taken from the adjacent proximal and distal ends. A twofold magnifying lens (Sunnex Laboratories) was then used to examine for the presence of mural thrombus formation. A thrombus may range in size from small numbers of aggregating platelets (1,8) to masses rich in various proportions of platelets, fibrin and red and white blood cells. We chose to look at macroscopic thrombus formation because easily visible thrombus has the potential of being physiologically and clinically relevant by embolizing, enlarging, obstructing blood flow or contributing to more severe vasoconstriction (9). Light microscopy was used to document the presence of a dissection or tear into the media.

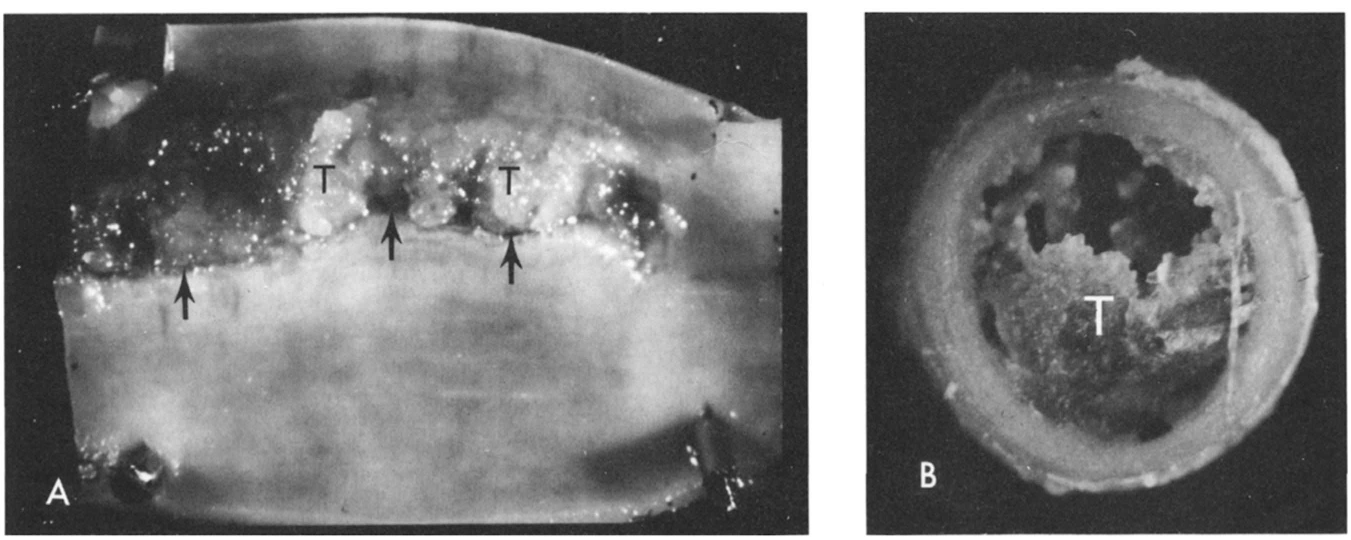
Although angiography provides a means of visualizing a tear or thrombus, it is insensitive and may not reflect the actual findings, which are better demonstrated by histopathologic examination. From each arterial segment, two to three ring sections were stained with hematoxylin-eosin and with Heidenhain's Weigert-van Gieson stain. The histologic sections were examined for the presence or absence of medial tears at the site of dilation. The consensus results of two observers were recorded. Because ecchymosis or hematoma is often seen in the adventitia of the dilated region, the surrounding connective tissue and adventitia were stripped from the artery during tissue preparation and before counting indium-111 in the gamma well counter. For scanning electron microscopy, two longitudinal specimens were cut from each segment, dehydrated through a series of ethanol solutions, dried with carbon dioxide and coated with gold-palladium and carbon. The intimal surfaces were then viewed with an Etec autoscan electron microscope. Endothelial damage and cell loss and their relation to the interaction of platelets and vessel wall were examined.

Quantitation of platelet deposition. The platelet deposition on each dilated artery (in millions per square centimeter) was calculated from platelet counts and indium-111 activity on the arterial wall and in the blood, as previously described (10). Three samples of blood obtained at the time of animal sacrifice were weighed in a microbalance, and the radioactivity per unit weight of each blood sample and per arterial segment (each one of which was measured for size) was obtained from a gamma well counter (Gamma 8000, Beckman) after correction for radionuclide decay. The spectrometer of the counter was adjusted to include the peaks at 174, 247 and 421 keV (sum peak) of the indium-111 radionuclide. The indium-111 counts per minute per gram of blood were transformed into counts per minute per milliliter of blood. The percent of radioactivity bound to platelets was then determined, and the number of platelets per counts per minute was calculated (10) from the known blood platelet count (Coulter counter). The number of platelets deposited on the arterial segments per square centimeter was then calculated by dividing the arterial segment counts per minute by both the number of platelets per counts per minute (10) and the arterial endothelial surface area (area = πdl, where d = diameter and l = length of the arterial segment).

Statistical analysis. Results were expressed as mean ± SEM. The statistical significance of the difference between the group means was evaluated by a two-tailed unpaired *t* test and a Fisher's exact test used for discrete variables. A separate analysis with exclusion of the two occluded arteries did not alter the statistical results.

Results

Thrombus formation. Within 1 hour of balloon angioplasty, a white mural thrombus was identified in 29 of the 56 dilated arteries at the site of dilation (Fig. 1A and B). These findings were confirmed on the histologic sections. Complete thrombotic occlusion of the arterial lumen occurred in two arteries where the luminal surface area of damage into the media appeared extensive but no intimal



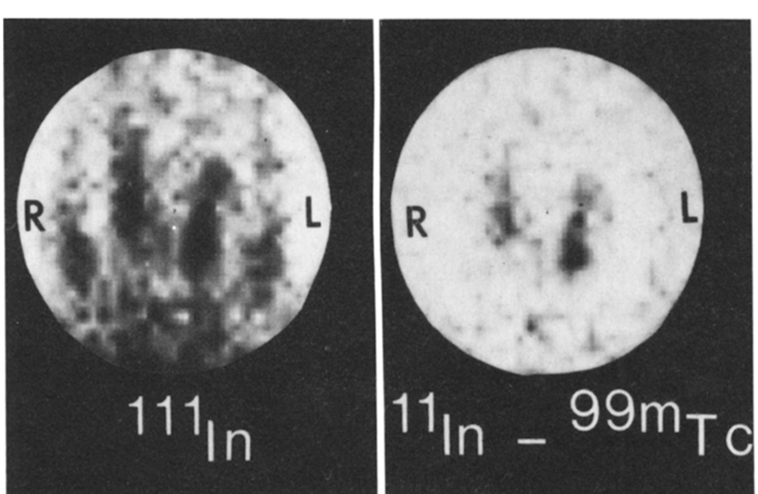


Figure 1. A, Endothelial surface of opened artery. Macroscopic platelet-mural thrombus (T) overlies a linear medial tear (**arrows**). **B,** Cross section of the artery shows a near occlusion by platelet thrombus (T). **C,** Indium-111–labeled platelet scintigram (^{111}In) (**left**) and indium-111 minus blood pool scintigram (^{111}In − ^{99m}Tc) (**right**). Thrombus present in both carotid arteries results in a clearly positive blood pool subtracted scintigram in the region of both carotid arteries. The jugular veins are visible laterally in the indium-111–labeled scintigram at **left**. L = left; R = right.

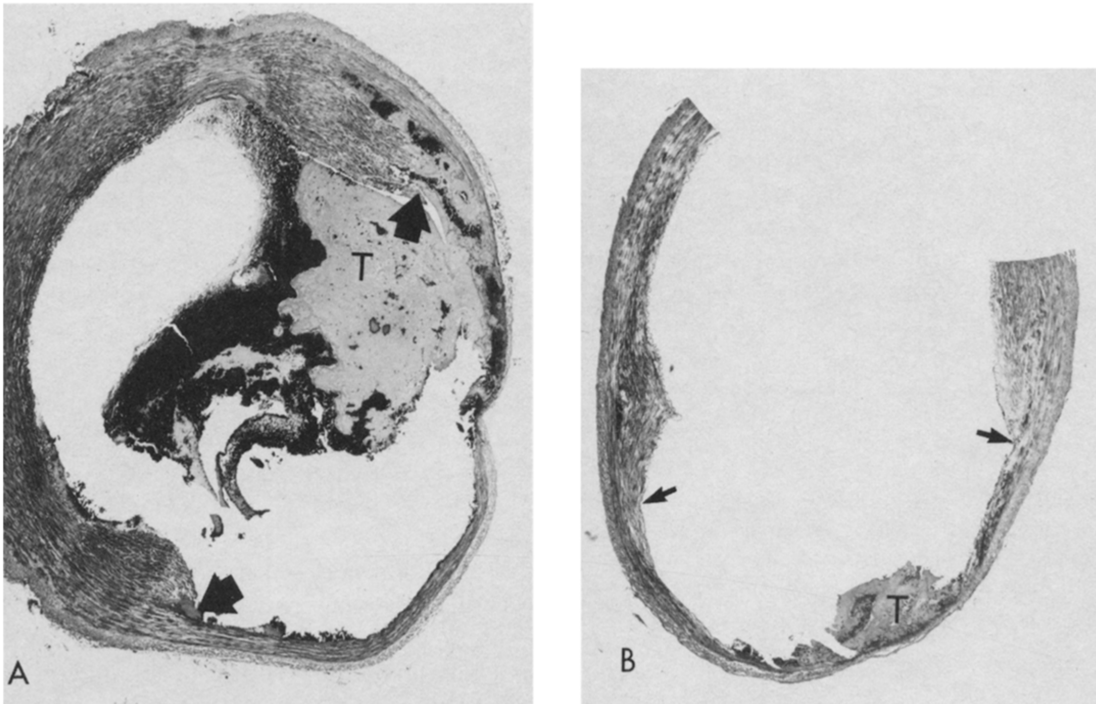


Figure 2. Sections of common carotid artery at site of dilation. Large and small thrombi (T) overlie the torn media. **Dark arrows** indicate the site of medial tears. **A,** A large thrombus may encroach on the lumen and restrict blood flow, and might be detected by multiplane angiography. **B,** A small thrombus may be missed angiographically. (Hematoxylin-eosin; original magnification × 40, reduced by 25%.)

variable extent. No tear or mural thrombus was seen in the nondilated areas distal to the site of the balloon-dilated segment where the endothelium remained intact. Complete endothelial cell loss but no mural thrombus was evident in the 24 dilated arteries without a medial tear ($p < 0.0001$).

Quantitative platelet deposition. In areas of balloon injury, platelet deposition averaged $67.5 \times 10^6/cm^2$, whereas flap was seen. No thrombus was evident in the nondilated distal areas. The baseline normal partial thromboplastin time averaged 23.8 ± 2.3 seconds before angioplasty and 98.5 ± 11.2 seconds at the time the animal was sacrificed, approximately 1 hour after administration of the heparin bolus.

Medial tear or dissection. With light microscopy, an intimal tear extending through the internal elastic lamina to involve various levels of the media was seen in 32 of 56 dilated arteries. This tear occurred at the site of balloon dilation and, in some cases, blood dissected circumferentially through the media. In 29 of the 32 tears, a mural thrombus was seen overlying the tear (Fig. 1A and 2) and encroaching on the arterial lumen (Fig. 1B and 2A) to a

in distal nondilated areas, it was less than $0.5 \times 10^6/cm^2$. This platelet deposition was significantly higher in the presence of a medial tear than it its absence (Table 1).

On scanning electron microscopy, platelets with marked pseudopodia formation were seen adherent to the dilated arterial segments where endothelial cell loss was evident. In the nondilated distal areas, the endothelium was intact and no adherent blood element was seen.

Correlation of platelet deposition, mural thrombosis and platelet scintigraphy. A platelet deposition in excess of 20×10^6 was associated with a thrombus that was visible macroscopically (with a 2× magnifying glass), whereas a deposition of less than 10×10^6 was not (Fig. 3). These intraarterial thrombi with platelet deposition in excess of

Table 1. Relation Between Medial Tear and Thrombus Formation

Medial Tear	Number of Arteries: Total	Number of Arteries: With Mural Thrombus	Platelets × $10^6/cm^2$: Mean ± SE
Yes	32	29* ($p < 0.0001$)	116.4 ± 26.5 ($p < 0.0008$)
No	24	0	7.0 ± 0.5

*Total occlusion in two (4%).

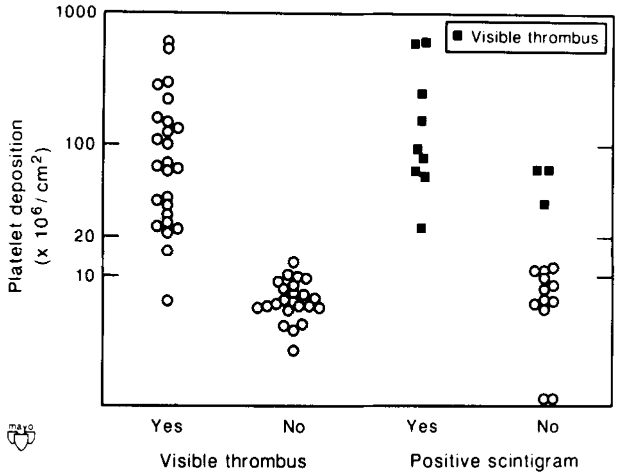


Figure 3. Relation of platelet deposition to visible thrombus and positive indium-111–labeled platelet scintigraphy combined with technetium-99m blood pool subtraction. Platelet deposition in excess of $20 \times 10^6/cm^2$ was associated with visible thrombus formation and a positive scintigram.

20×10^6 can also be scintigraphically imaged in vivo and noninvasively by use of indium-111–labeled platelet scintigraphy combined with technetium-99m blood pool subtraction imaging (Fig. 1C). In the 12 pigs imaged, all 12 arteries with a thrombus had a platelet deposition in excess of $20 \times 10^6/cm^2$, and a positive image was obtained in 9. In the three arteries with thrombus but a negative scintigram, the thrombus was more diffuse and spread over a greater surface area. The other 12 arteries, with a platelet deposition less than $20 \times 10^6/cm^2$, had neither a thrombus nor a positive scintigram.

Discussion

By denuding the endothelium, balloon injury of an atherosclerotic or normal arterial segment (11,12) provides a potent stimulus for extensive platelet deposition at the site of vessel wall injury. This platelet deposition may progress to a platelet-thrombus formation that may partially or totally occlude the arterial lumen and thus may compromise the result of an otherwise successful balloon angioplasty (2,13). In this study, we have shown that a positive in vivo indium-111–labeled platelet scintigram indicates the presence of macroscopic mural thrombus and deep arterial injury.

Determinants of thrombus formation and positive scintigram. Arterial injury during angioplasty led to platelet deposition as determined both qualitatively and quantitatively. More important, deep arterial injury through the internal elastic lamina in 57% of the dilated arteries was associated with macroscopic thrombus formation and very high platelet deposition in 91% of the dissected arteries within an hour of the procedure, despite adequate heparin therapy (partial thromboplastin time far in excess of 2.5 times baseline) begun before the procedure. In contrast, dilated arteries without a medial tear all had much less platelet deposition and no evidence of thrombus formation at the site of endothelial loss. Production of deep arterial injury during angioplasty thus appears to be the major factor leading to macroscopic thrombus formation. Factors associated with the production of a medial tear were not addressed in this study, but may in part be related to balloon and lumen size, inflation pressure, duration of inflation, number of inflations and location and extent of disease in the artery.

Platelet deposition leading to macroscopically visible thrombus and a positive, noninvasive, in vivo, indium-111–labeled platelet scintigram occurred when the platelet deposition was localized and greater than $20 \times 10^6/cm^2$. Thus, this technique may be potentially useful for noninvasive in vivo detection of clinically important arterial thrombus formation, which may identify a high risk of acute occlusion or restenosis. It may also provide a noninvasive test for the in vivo efficacy of antithrombotic therapy, such as administration of platelet inhibitor drugs or thrombolytic agents.

Possible mechanisms of thrombus formation. Severe arterial wall injury with exposure of the media appears to represent a very thrombogenic stimulus that is much greater than deendothelialization alone (14,15). This enhanced thrombogenesis likely involves platelet interaction with connective tissue components of the arterial wall, such as collagen, and the activation of both the intrinsic (16,17) and extrinsic (18) coagulation pathways, leading to formation of thrombin and fibrin (14,15). Thrombin contributes to platelet activation, and fibrin stabilizes the platelet aggregate (14,15). Honour et al. (19) showed that the degree of injury is an important determinant for thrombus formation, and damage to both the endothelium and the media invariably occurred when a mural thrombus was formed. Platelets release reaction, important for platelet aggregation, is facilitated more by adherence to the deeper fibrillar collagen (20,21) than by adherence to the subendothelial basement membrane (20).

In addition, factors inhibiting thrombus formation and promoting thrombus dissolution appear to be inactivated after vessel wall injury. Tissue plasminogen activator derived from intact endothelium is lost with endothelial denudation at the site of injury (22). Consequently, the capacity for plasmin generation, fibrinolysis and thrombus dissolution is decreased. Vessel wall injury may also destroy the proteoglycans that inactivate thrombin (23), destroy the vessel wall adenosine diphosphatase that inactivates proaggregatory adenosine diphosphatase (24) or destroy thrombomodulin, the endothelial cell cofactor involved in the activation of protein C (25), a natural anticoagulant. The vessel wall generation of prostacyclin (PGI_2), an important inhibitor of thrombus formation (26,27), is also decreased (28).

Animal model: angioplasty of normal versus atherosclerotic stenotic arteries. Although potential problems can be raised in trying to extrapolate the results of our studies in pigs to clinical angioplasty in humans, pigs appear to be a good model for the study of thrombosis and atherosclerosis. The platelet response in pigs closely approximates that in humans (29). Fibrocellular atherosclerotic plaques occur naturally without dietary manipulation or in an accelerated fashion with dietary manipulation and closely resemble those in humans (30,31). Because our studies were done with normal arteries, it is possible that the reponse of atherosclerotic vessels to angioplasty may differ, but any difference probably is only in an increased degree of response due to the inevitable plaque rupture necessary for a successful angioplasty (3,4) and the release of thrombogenic lipid gruel (15).

In clinical angioplasty, the arterial luminal diameter may be narrowed to about 1 mm at the site of stenosis, and a 3 mm balloon may be used to dilate that stenotic segment and approximate the luminal diameter adjacent to the stenosis. Although the balloon may be matched for the artery, at the site of stenosis, the balloon is relatively larger (on the order of 3 to 1) than the lumen. Because there was no focal stenotic segment to be dilated in our model, a bigger balloon than would otherwise be necessary was used (8 mm balloon for a 5 to 6 mm arterial luminal diameter). However, the diameter of the balloon inflated within the artery was only 9.1 ± 6.0% (mean ± SD) more than the diameter of the artery, as measured from spot films taken before and during balloon inflation. If a focal stenosis had narrowed the arterial lumen to 2 mm, a 5 to 6 mm balloon would have been used. Thus, arterial injury produced in this study may be less than that in clinical angioplasty where plaque splitting occurs not uncommonly (2–4) and is associated with a high complication rate, which may be related in part to thrombus formation.

Because a successful angioplasty in human patients almost certainly must involve plaque splitting and exposure of fibrillar collagen and smooth muscle cells to flowing blood (3,4), a very high incidence of mural thrombosis would be expected in human atherosclerotic arteries, probably even greater than the 56% we found in normal pig arteries after angioplasty. However, our sensitivity for detection of arterial injury and mural thrombosis is much lower in humans by angiography than in pigs by histology. A tear through a plaque or an atherosclerotic vessel would likely be no less, if not more, thrombogenic than a tear through a normal artery. In this regard, Stevenson et al. (32) showed that the thromboplastic activity of an atherosclerotic intima is greater than that of normal intima. Also, Lyford et al. (33) demonstrated the enhanced coagulant and platelet-clumping properties of atheromatous plaques. Stemerman (11) showed that balloon injury to the vessel wall produces an exaggerated thrombotic response, with atherosclerotic plaque injury, compared with that in normal arteries. Although thrombosis can occur spontaneously in areas of atherosclerotic plaques (34), it is likely that plaque fissuring or rupture makes an important contribution to this thrombus formation (35,36).

Clinical implications. After deep arterial wall injury with a tear into the media, there is mobilization of factors promoting thrombus formation and destruction of factors inhibiting thrombus formation or promoting thrombus dissolution. Overall, these contribute to the marked thrombogenicity observed at the site of deep injury. Because thrombus formation begins during the procedure and may lead to early occlusion (1,11) and later restenosis (1), or contribute to vasoconstriction (9) after angioplasty, it seems reasonable to test potentially successful antithrombotic therapy by administering it before the procedure and continuing it during and after the procedure. Dual isotope scintigraphy may provide a means of detecting this in vivo platelet-thrombus formation, which may cause acute occlusion. It may also permit noninvasive evaluation of the efficacy of platelet inhibitor or thrombolytic therapies. However, at least 20×10^6 platelets/cm^2 must be present in the thrombus for successful imaging.

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